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Multifocal Vasculopathy Due to Varicella-Zoster Virus (VZV): Serial Analysis of VZV DNA and Intrathecal Synthesis of VZV Antibody in Cerebrospinal Fluid

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Recognition of multifocal vasculopathy due to varicella-zoster virus (VZV) is often problematic. We describe a human immunodeficiency virus–infected patient who had progressive central nervous system disease for >3 months. Both VZV DNA and antibody were detected in cerebrospinal fluid (CSF) specimens; serial polymerase chain reaction analyses confirmed the diagnosis and guided the duration of therapy. Reduced ratios of VZV antibody in serum to that in CSF were also demonstrated.

Multifocal vasculopathy due to varicella-zoster virus (VZV) is often difficult to recognize because neurological symptoms and signs can assume many forms and because brain imaging studies reveal multifocal lesions similar to those seen with cerebral emboli, metastases, lymphoma, and toxoplasmosis. We describe an HIV-infected patient with progressive CNS disease who was determined to have multifocal vasculopathy due to VZV.

Case report. A 28-year-old man who was infected with HIV and hepatitis C virus was hospitalized for progressive dizziness of 3 months' duration and recent-onset left-side weakness. Nine months earlier, his CD4 cell count was 13 cells/ μ L and his HIV load in serum was 92,029 copies/mL. When dizziness and vertigo developed, the patient underwent neurolog-

ical examination and CT of brain, the findings of which were normal. Two weeks before admission, the patient began receiving antiretroviral therapy with lamivudine (150 mg b.i.d.), zidovudine (300 mg b.i.d.), nelfinavir (1250 mg b.i.d.), and trimethoprim-sulfamethoxazole (160 mg/800 mg 3 times per week). His medical history was otherwise unremarkable; he never developed cutaneous herpes zoster. On admission, he was afebrile. Neurological examination revealed left-side mydriasis without ptosis or anhidrosis, a left-side hemiparesis and homonymous hemianopia, and neglect to the left. Laboratory studies revealed a hemoglobin level of 9.1 g/dL, a WBC count of 2550 cells/ μ L, and a normal platelet count. C-reactive protein and serum electrolyte levels were normal, and the findings of chest radiography and of liver and renal function studies were normal.

CT of brain revealed contrast-enhancing lesions in the right occipitotemporal and parieto-occipital cortices (figure 1A). MRI of the brain corroborated the vascular distribution of the lesions and also revealed prominent subcortical edema (figure 1B, 1C); a small signal of uncertain significance, which was possibly ischemic, was also seen close to the right lateral ventricle (figure 1B). The findings of magnetic resonance angiography were normal.

Analysis of CSF specimens obtained from the patient revealed 11 WBCs/mm³ (95% mononuclear), a protein level of 135 mg/dL, and a normal glucose level. The results of Venereal Disease Research Laboratory testing of CSF specimens were negative; culture of CSF specimens revealed no bacteria, including mycobacteria; and no cryptococcal antigen or *Toxoplasma*-specific IgG was detected. Serum was also negative for IgG antibody to *Toxoplasma*. PCR analysis of CSF specimens with primers specific for bacterial 16S RNA [1] and *Toxoplasma* species, cytomegalovirus, Epstein-Barr virus, herpes simplex virus types I and II, and JC virus DNA were negative. However, PCR with primers specific for VZV glycoprotein I gene (open-reading frame 67) amplified VZV DNA. PCR was done with use of TaqMan chemistry and the following sequences: 5'-ACAGCTTGCTTTATTGGAGAGCAA-3' as the forward primer, 5'-GCCACCGTATCCGCGTATA-3' as the reverse primer, and 5'-(FAM)-ACCTACCGGGACAACTATAGCGGAACACTG-(TAMRA)-3' as the probe. Furthermore, VZV antibody analysis indicated a decrease in the ratio of VZV-specific IgG in serum to that in CSF to 0.89, compared with ratios of 39 for albumin and 44 for total IgG, which is consistent with intrathecal synthesis of VZV-specific IgG [2].

Because encephalitis due to *Toxoplasma* species could not be

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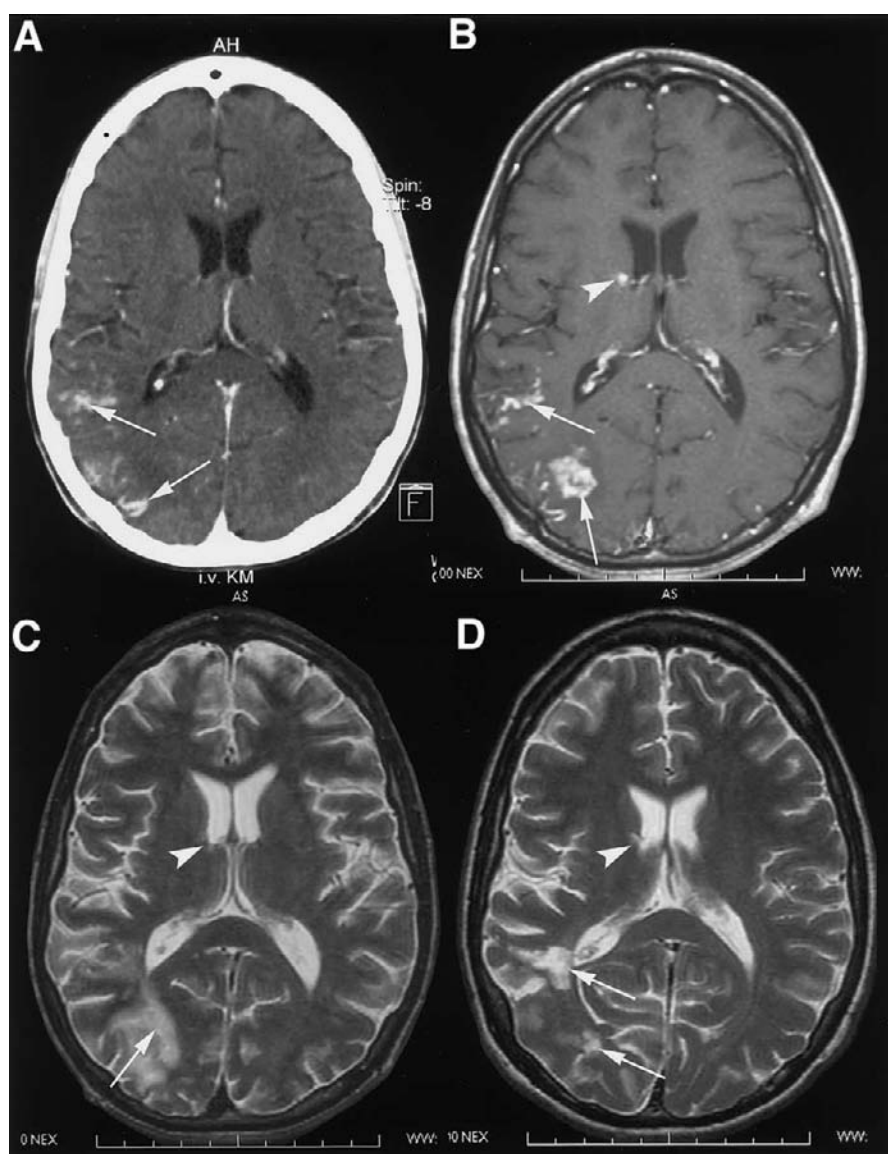


Figure 1. A, Contrast-enhanced CT of the brain of a patient with varicella-zoster virus multifocal vasculopathy showing contrast-enhancing lesions (arrows) in right occipitotemporal and parieto-occipital cortices. B, MRI of brain showing 2 lesions (arrows) in right occipitotemporal and parieto-occipital cortices. A small contrast-enhancing lesion, which is possibly ischemic, is visible close to right lateral ventricle (arrowhead). C, T2-weighted MRI showing subcortical edema (arrow) extending into optic radiation and a small area of increased signal adjacent to internal capsule and frontal horn (arrowhead). D, T2-weighted MRI from 5 months after treatment revealing residual right posterior hemispheric infarcts (arrows) and a small CSF-filled infarct close to lateral ventricle (arrowhead).

excluded initially, the patient was treated empirically with sulfadiazine (1500 mg q.i.d.) and pyrimethamine (75 mg q.d.). On detection of both VZV-specific DNA and antibody in CSF specimens, the diagnosis of VZV multifocal vasculopathy was confirmed, and the patient was treated with intravenous acyclovir (10 mg/kg t.i.d.) for 24 days. Treatment efficacy was monitored by serial real-time PCR analysis of CSF specimens. A 4-log reduction in the number of VZV DNA copies (from $\geq 10^4$ copies/mL [day 0] to 5×10^1 copies/mL [day 14] and to $< 10^1$ copies/mL [day 21]) was observed when all CSF samples

were analyzed in parallel. After receiving intravenous acyclovir treatment for 21 days, the patient had no neurological symptoms, and the results of PCR of CSF specimens for VZV DNA were negative. Acyclovir therapy was discontinued 3 days later, and a 4-week course of oral valacyclovir (2000 mg t.i.d.) was begun. Five months after the initiation of valacyclovir therapy, the findings of a neurological examination were normal, and MRI performed at this time showed residual cortical infarcts (figure 1D).

Discussion. In the past decade, the protean clinical features

of VZV multifocal vasculopathy have been well characterized [3]. Most, but not all, patients are immunocompromised, usually because of AIDS, and disease is often protracted and may progress without rash [4–7]. Symptoms and signs include combinations of headache, fever, mental status changes, seizures, and focal deficit. Brain imaging studies reveal both large and small infarcts of both cortical and subcortical gray and white matter; infarcts are usually ischemic [8, 9] but may also be hemorrhagic [10]. In this regard, the diagnosis of VZV vasculopathy might have been recognized earlier for our patient had contrast-enhanced MRI initially been performed instead of CT. Testing of CSF specimens usually yields nonspecific results, showing increased WBC count (predominantly mononuclear cells), with elevated protein and normal glucose levels. Although diagnosis can be difficult to make when the patient lacks a history of rash, it is important to recognize that rash is often absent from patients with CNS disease caused by VZV. A retrospective analysis of 34 HIV-infected patients with cerebral VZV infection showed that 17.6% of the patients never developed rash [11]. Nevertheless, the multifocal changes detected on brain imaging studies should mandate the need for virological analysis to confirm that VZV is the cause of disease. In the aforementioned clinical setting, the detection of VZV DNA and/or antibody to VZV in CSF specimens verifies the diagnosis of VZV-induced multifocal vasculopathy [12]. Similar virological analyses have shown that VZV also causes acute, chronic, and recurrent myelitis [13], as well as acute, chronic, and recurrent neuropathies [14], often without rash, including chronic radicular pain without rash (the so-called “zoster sine herpete”) [15].

In our patient, both VZV DNA and antibody to VZV were detected in CSF specimens. Also, serial PCR analyses to monitor VZV DNA in CSF over time not only confirmed the diagnosis, but they also guided the duration of therapy, which led to a beneficial outcome for our patient. As described elsewhere in a study of 3 children with VZV-associated cerebral vasculitis [16], decreased ratios of antibody to VZV in serum to that in CSF were demonstrated, providing definitive evidence for the viral etiology of disease in our patient. Detection of reduced ratios of antibody to VZV in serum/CSF has been critical for the diagnosis of VZV autonomic neuropathy [17] and VZV myelitis [18, 19]. Previous antibody studies of cases of VZV vasculopathy revealed high titers of antibody to VZV in CSF specimens, which emphasizes the diagnostic value of detecting VZV antibody in CSF, even when viral DNA is not present [19]. However, the ability to demonstrate reduced ratios of antibody in serum to that in CSF in our patient was the linchpin in our diagnosis that VZV caused the multifocal vasculopathy.

No controlled studies have addressed the duration of antiviral treatment necessary to treat VZV multifocal vasculopathy. The duration of treatment for HIV-infected patients has ranged

from 7 to 60 days [11]. Monitoring of VZV DNA in CSF and of intrathecal antibody production should help to establish guidelines for the duration of antiviral treatment to protect patients from recurrent disease. It is unlikely that antiretroviral therapy contributed essentially to the recovery in our patient, because antiretroviral therapy was initiated only 2 weeks before acyclovir therapy.

Finally, clinicians must be alert to the clinical manifestations of VZV multifocal vasculopathy, the characteristic abnormalities visible on MRIs, and the importance of confirming the diagnosis by virological analysis of CSF specimens. Although multiple areas of the brain are affected, VZV-induced multifocal vasculopathy is not a primary encephalitis (i.e., parenchymal infection) but rather a productive VZV infection, mostly or exclusively restricted to cerebral arteries [6, 9, 20–23]. This fact emphasizes the need for rapid diagnosis and antiviral treatment to eradicate virus in arteries and to prevent further stroke. The failure of clinicians to recognize the entity of VZV-induced multifocal vasculopathy was evident in a recent review in which the causes of focal neurological disease in patients with AIDS were listed as *Toxoplasma gondii*, progressive multifocal leukoencephalopathy, cytomegalovirus, and Epstein-Barr virus–related CNS lymphoma, without any mention of VZV multifocal vasculopathy [24].

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